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Pseudopatients

Simulated patients—people trained to simulate the histories, the symptoms, and physical signs of actual cases—have been successfully used in medical education[1-3] since 1962. Professor H. Barrows, the pioneer of this imaginative idea, rather naively suggested[2] that simulated patients could also be used to evaluate the care received in hospitals and doctors' practices. The advantages, he claimed, would be objectivity and consistency—but he did not even hint at the objections.

The other side of the argument was clearly presented in a recent analysis[4] by an Australian psychiatrist, Professor N. McConaghy, of the use of pseudopatients to investigate treatment, hospital care, and psychiatric diagnosis. Pseudopatients differ from simulated patients in that they are not trained in the art of simulation and may well lack objectivity and consistency. In this trenchant article the main target was the paper published in *Science* by Professor D. L. Rosenhan,[5] a psychologist from Stanford University, California, which created a brief stir last year. Rosenhan had described how he and seven others gained admission to 12 different psychiatric hospitals by saying that they had been hearing voices. Only in Rosenhan's case was the plan known to the authorities. Though all "symptoms" ceased on admission (apart from some apprehension of being exposed as frauds and of their unfamiliar surroundings) none of the pseudopatients asked to be discharged. They were in fact in hospital for periods ranging from seven to 52 days, and though their fellow patients suspected their bona fides—largely because they spent so much time making notes—the staff did not.

Rosenhan criticized the system of psychiatric diagnosis and the ease of labelling, but, as McConaghy pointed out, the false clues—no return of symptoms, normal behaviour but no request for discharge—made schizophrenia in remission much the likeliest explanation of their symptoms. He went on to criticize the author for making "no attempt to control for the bias of the pseudopatient role or indeed, and more importantly, for his own"—criticisms that applied equally, he thought, to two other articles reporting the use of pseudopatients published in the same issue of the *Medical Journal of Australia*.

In the first of these[6] four clinical psychology graduates gained admission, by presenting false case histories, to major Sydney psychiatric hospitals. They reported on the attitude of the staff to patients and to patients' complaints about the (they claimed) excessive use of drugs and about the universal boredom. In the other[7] pseudopatients giving a history of "a depression of psychosocial origin" presented themselves to 25 general practitioners in the Sydney area. The treatment recommended ranged from discussion and counselling to referral to either a psychiatrist or a social worker, but the commonest was a prescription for some drug. When a psychotropic drug was prescribed no advice about the possible side effects was offered to 57% of people.

In the evaluation of medical care pseudopatients could provide simple facts of this kind and, for another example, the amount of time that a psychiatric patient in hospital spends with doctors. But caution is needed. What appears as boredom to the healthy pseudopatient may be peace and quiet to the depressive; an offer of a sleeping pill to a pseudopatient may be criticized as unnecessary, whereas many real patients in need of one might not ask. The answers to more complex questions, inquiries about attitudes and concepts, roles, and relationships, are much more at the mercy of the prejudices of the pseudopatients and of those who plan the investigation.

McConaghy's criticism of these three reports, forceful though it was, was by no means comprehensive. Other criticisms apply as much to simulated, trained, observing "patients," free of bias, as to pseudopatients. These people divert resources from those in need; the good will of nurses and others is abused; there is a sowing of distrust, and a new and unwelcome element is added to differential diagnosis. Above all, what reliance can be placed on the conclusions of an inquiry that begins with deceit and lies?

Evaluation of hospital care and medical practice is certainly necessary. In psychiatry (remember Ely, Whittingham, Farleigh, and South Ockenden) it is needed most in fields in which the pseudopatient could not flourish—subnormality, chronic psychosis, and psychogeriatrics. But how can this evaluation best be obtained? The well-publicized pseudopatient project of the National Association for Mental Health[8] —one M.P., a former M.P. and junior minister, and two others went in 1971 into four psychiatric hospitals for 72 hours—is open to some of the criticisms already made, but not all since their role was known to doctors and senior nurses.

But if pseudopatients cannot tell us what life is like on a psychiatric ward, how otherwise can we learn? From genuine patients? The painstaking investigation by questionnaire, such as that sponsored by the King's Fund,[9 10] has improved conditions in hospitals that have taken it up. Its weakness is that hospitals that undertake such surveys are likely to be self-selective; the worst-run ones will do nothing. Are we then to rely on the old-fashioned method of visiting? The visits of the Hospital Advisory Service, though announced in advance, are undoubtedly effective in showing up deficiencies and in

improving standards; but many psychiatrists look back nostalgically to the Board of Control in its heyday. However, even if questionnaires cannot reach the least articulate and most defenceless and visiting teams are too far removed from what goes on in the wards the pseudopatient has no place at all in evaluation. His relationship with doctor and nurse is false, and because he is not a patient much of the information he obtains is likely to be either false or could be more simply obtained in other ways. The biased pseudopatient finds, as McConaghy says, what he expects to find and proves nothing.

[1] Barrows, H. S., and Abrahamson, S., *Journal of Medical Education*, 1964, **39**, 802.
[2] Barrows, H. S., *Simulated Patients*, ed. Charles C. Thomas. Springfield, Illinois, 1971.
[3] *British Medical Journal*, 1974, **2**, 399.
[4] *The Medical Journal of Australia*, 1974, **2**, 383.
[5] Rosenhan, D. L., *Science*, 1973, **179**, 250.
[6] Winkler, R. C., *The Medical Journal of Australia*, 1974, **2**, 399.
[7] Owen, A., and Winkler, R., *The Medical Journal of Australia*, 1974, **2**, 393.
[8] *Life on a Psychiatric Ward*. London, National Association for Mental Health, 1971.
[9] *Psychiatric Hospitals Viewed by their Patients*. By Winifred Raphael and Valerie Peers. London, King Edward's Hospital Fund, 1972.
[10] Raphael, W., *Survey of Patients' Opinion Surveys in Hospital*. Project Paper No. 9. London, King Edward's Hospital Fund, 1974.

Endotoxaemia

The increasing incidence of Gram-negative septicaemia[1 2] has led to much debate about the pathogenesis of the associated shock, which is often related to endotoxin released from the bacteria in the bloodstream. Where endotoxin is given to some animal species there are marked cardiovascular changes[3-6] leading to impaired tissue perfusion. Other phenomena,[7] including the generalized Schwartzmann reaction, have been described, and the injection of large doses of endotoxin derived from Gram-negative bacteria can be fatal in animal experiments.

The clinical presentation of Gram-negative shock in man shows so many resemblances to the changes in animals undergoing endotoxic shock that it is reasonable to suggest that the two are the same.[7] However, some workers[8] have questioned this conclusion and have suggested that other microbial fractions may be more important than endotoxin in the production of Gram-negative shock. Certainly patients may suffer from Gram-negative shock and have no evidence of circulating endotoxin demonstrable by the limulus test.[9] Furthermore, shock clinically indistinguishable from endotoxaemic shock is occasionally produced by Gram-positive organisms such as staphylococci, which clearly lack endotoxin.

The source of the Gram-negative bacilli causing endotoxic shock is usually clear when it occurs in a patient with a condition such as urinary tract infection or cholecystitis. It is more difficult to understand the pathogenesis of endotoxic shock in experiments where shock induced by non-septic conditions such as trauma is accompanied by endotoxaemia. Fine and his colleagues postulated that after trauma or burns vasoactive substances might be released which increased the permeability of the gut wall to endotoxin. In their most recent series of experiments[10] endotoxaemia was demonstrated within two hours of induction of a moderate sized burn in rabbits. Within 10 to 12 hours a severe plasma volume deficit occurred, leading to vascular collapse and death. The critical role of the Gram-negative flora in the intestine was established by the fact that the fatal endotoxaemia did not occur in rabbits lacking these bacteria (why some animals had a Gram-negative or Gram-positive intestinal flora was not made clear). Next venous blood which did not contain endotoxin was taken from burned rabbits and given to normal recipients, which then suffered fatal endotoxaemia. These experiments indicated that a substance was released from a burn which mobilized endotoxin from the gut. Further evidence that the endotoxin originated in the gut was obtained from isolation of endotoxin in the peritoneal fluid of the burned animals.

The endotoxaemia could be prevented by efficient fluid and electrolyte therapy and controlled by intra-aortic corticosteroids. Fine *et al.* suggested that these measures helped to prevent hypovolaemia and thereby reduced liver ischaemia. When the liver is adequately perfused any endotoxins released into the portal circulation from the gut will be cleared and so fail to reach the systemic circulation. If the liver is ischaemic the endotoxin passes through.

So far much of the experimental work in support of the idea that endotoxic shock may follow non-septic conditions has come from Fine's laboratory in Boston. These latest experiments might stimulate other laboratories to investigate the relationship of endotoxaemia to shock due to trauma and burns. The measurement of endotoxin remains difficult, however, and there is a need for a sensitive method more practicable than the limulus test.

[1] Finland, M., *Journal of Infectious Diseases*, 1970, **122**, 419.
[2] Nauman, P., *Bayer Symposium*, 1971, **III**, 37.
[3] Maclean, L. D., and Weil, M. H., *Circulation Research*, 1956, **4**, 546.
[4] Lillehei, R. C., *et al.*, *Annals of Surgery*, 1964, **160**, 682.
[5] Lillehei, R. C., *et al.*, *Clinical Pharmacology and Therapeutics*, 1964, **5**, 682.
[6] Zweifach, B. W., in *Bacterial Endotoxins*, ed. M. Landy and W. Braun, p. 110. New Brunswick, Rutgers University Press, 1964.
[7] Glynn, A. A., and Howard, C. J., in *Recent Advances in Clinical Pathology*, ed. S. C. Dyke. Edinburgh, Churchill-Livingstone, 1973.
[8] Kass, E. H., *et al.*, *Journal of Infectious Diseases*, 1973, **128**, S299.
[9] Levin, J., *et al.*, *New England Journal of Medicine*, 1970, **283**, 1313.
[10] Cuevas, P., *et al.*, *Surgery, Gynecology and Obstetrics*, 1974, **138**, 725.

Drug Targets in Cancer Chemotherapy

One of the topics of the recent XIth International Cancer Congress in Florence was the design of anticancer drugs aimed at enzymes and isoenzymes. Many effective antimetabolites used for cancer chemotherapy act directly on or indirectly through enzymes which catalyse steps in the synthesis of DNA. Drugs that are analogues of enzyme substrates can very often pass through several enzymatic stages of a biosynthetic pathway before reaching an enzyme which accepts the rogue metabolite but cannot effect a further conversion. The enzyme then becomes blocked to the normal substrate.

C. Heidelberger reviewed studies on 5-fluorouracil, perhaps one of the most successful antitumour agents to arise out of research applying these logical principles. The drug is converted by three alternative pathways to 5-fluoro-2-deoxyuridylic acid, which is a powerful competitive inhibitor of thymidylate synthetase.[1] This enzyme converts deoxyuridylic acid into thymidylic acid—an essential and thus rate-limiting step in DNA synthesis. One of the effects of methotrexate is to inhibit this same step, but it does so by inhibiting the enzymatic production of the cofactor required, tetrahydrofolate.[2] In some instances such as 6-thioguanine and 6-mercaptopurine the nucleotide antimetabolites succeed in passing through the entire biosynthetic chain and inhibit the